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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,808	11/14/2003	Dave S.B. Hoon	JWCI 0035 PUSP	4483

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/713,808	HOON ET AL.	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,10,35-38 and 40-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7, 10, 35-38, and 40-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 5/7/10 in response to the Office Action of 4/15/10 are acknowledged and have been entered.

Claims 48-63 have been added by Applicant.

Claims 1-5, 7, 10, 35-38, and 40-63 are pending.

Claims 1, 35, and 36 have been amended by Applicant.

Claims 1-5, 7, 10, 35-38, and 40-63 are currently under examination.

Response to Arguments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, 7, 10, 35, 36, 38, and 40-44 remain rejected and claims 48, 50-53, 55-57, and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoon et al (US Patent 6,057,105; 5/2/00) in view of Scholl et al (2/01, Cancer Research, 61:823-826) for the reasons stated in the Office Action of 11/4/09, for the reasons stated in the Office Action of 4/15/10, and for the reasons set-forth below.

Hoon et al teaches a method of detecting circulating melanoma cells comprising: (a) isolating nucleic acid from a sentinel lymph node (SLN) sample, tumor draining lymph node sample, or blood sample obtained from a melanoma patient; (b) amplifying

mRNA transcripts encoded by GalNAcT, MAGE-3, and MART-1 marker genes from the nucleic acid from the SLN sample, tumor draining lymph node sample, or blood sample obtained from the melanoma patient wherein amplification is done by PCR; (c) detecting the levels of GalNAcT, MAGE-3, and MART-1 mRNA transcripts in the nucleic acid from the SLN sample, tumor draining lymph node sample, or blood sample obtained from the melanoma patient; and (d) comparing levels of the mRNA transcripts encoded by the GalNAcT, MAGE-3, and MART-1 marker genes in nucleic acid from a SLN, tumor draining lymph node sample, or blood sample obtained from a second melanoma patient to levels of mRNA transcripts encoded by the GalNAcT, MAGE-3, and MART-1 marker genes in the nucleic acid from the SLN sample, tumor draining lymph node sample, or blood sample obtained from the first melanoma patient to determine melanoma status (see lines 15-19 of column 3, claim 69, and lines 57-59 of column 41, in particular), assigning a clinical melanoma stage to the subject (column 38 lines 45-51 and column 40 lines 4-6, in particular), predicting recurrence (Figure 1 and column 38 lines 60-65, in particular), predicting survival of the subject (Figure 1, in particular), and monitoring melanoma progression or treatment response (column 21 lines 41-60 and column 14 lines 41-59, in particular). It is noted that "MAGE-3" is an alternate name of "MAGE-A3" as recited in the instant claims. The method taught by Hoon et al further comprises predicting melanoma recurrence or survival of the subject for a period of greater than 30 months following removal of a primary tumor, SLND, or both (Figure 1, in particular). The method taught by Hoon et al further comprises samples wherein the histopathology of the body fluid or tissue sample is determined by H&E and would

determine whether the SLN or blood sample from the subject is histopathologically positive of negative for melanoma cells (Example VII, in particular). Hoon et al further teaches a method wherein a high number of genes expressed indicates an advanced melanoma stage, progression or melanoma, a high probability of melanoma recurrence, or a low probability of survival (Figure 1, in particular). Hoon et al further teaches a method wherein the samples are frozen (see Example VII, in particular). In the method of Hoon et al, the detection of GalNac-T, MAGE-3, and MART-1 in a sample from a subject, as compared to a subject without detected GalNac-T, MAGE-3, and MART-1, "upstages" a prognosis and correlates with melanoma recurrence and shorter relapse-free survival because detection indicates the presence of circulating melanoma cells. Further, the abstract of Hoon et al states "Methods using multiple markers provide increased sensitivity over existing methods" and Example XIII of Hoon et al states "None of the markers alone would have been able to detect cancer cells in all of the specimens. This variation in marker detection reflects the heterogeneity of tumor cells. In conclusion, multiple markers are more sensitive to detection of breast cancer than any one marker". Further, subjects expressing a higher number of melanoma-specific markers (such as GalNac-T, MAGE-3, and MART-1) in samples would be expected to be worse off than patients expressing a lower number of melanoma-specific markers because those expressing a lower number of melanoma-specific markers would include those that express no markers, as well as false-positive results, and subjects with a higher number of detected (above zero copy number) melanoma-specific markers would more accurately detect circulating melanoma cells in subjects that have a higher

likelihood of recurrence and shorter relapse-free survival as compared to patients expressing a lower number of detected (above zero copy number) melanoma-specific markers which do not have circulating melanoma cells.

Hoon et al does not specifically teach PAX-3 being part of the panel of genes used. However, this deficiency is rendered obvious or made up in the teachings of Scholl et al.

Scholl et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from a patient, amplifying nucleic acid targets from a panel of marker genes comprising PAX-3 and MAGE-A3, and detecting the presence or absence of the nucleic acid targets (Table 1 and Table 2, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to perform the method of detecting and characterizing metastatic melanoma as taught by Hoon et al with a panel of genes comprising PAX-3 because Hoon et al teaches incorporating nucleic acids of any melanoma markers into the panel (see column 3 line 9-14, in particular) and Scholl et al teaches PAX-3 nucleic acid is a melanoma marker (see Table 1 and Table 2 of Scholl et al, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success when performing the method taught by Hoon et al with a panel of genes comprising PAX-3 because Scholl et al has demonstrated that PAX-3 nucleic acid is a marker of metastatic melanoma (see Table 1 and Table 2 of Scholl et al, in particular). Further, Scholl et al teaches PAX-3 and MAGE-A3 are overexpressed in

metastatic malignant melanoma cells in vivo (pages 825-826, in particular) and Hoon et al teaches GalNAc-T, MAGE-A3 (MAGE-3), and MART-1 are also overexpressed in metastatic melanoma cells in vivo (column 2 line 53 to column 3 line 36, lines 15-20 of column 3, and Example IV, in particular). Since Scholl et al and Hoon et al teach overlapping panels of genes that are overexpressed in the same type of sample (metastatic melanoma cells) and Hoon et al teaches metastatic melanoma cells would be detected in body fluid samples (column 2 line 53 to column 3 line 36 and Example IV, in particular), one of skill in the art would expect PAX-3 to be overexpressed by metastatic melanoma cells in body fluid comprising metastatic melanoma cells. Further, one of skill would expect said melanoma recurrence and survival would be predicted for a period of at least three years following removal of a primary tumor, SLND, or both by detecting GalNAc-T, MAGE-A3, and MART-1 because Hoon et al teaches said melanoma recurrence and survival would be predicted for a period of at least 30 months following removal of a primary tumor, SLND, or both by detecting multiple markers of circulating melanoma cells including MAGE-A3 (Figure 1, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

In the Reply of 5/7/10, Applicant states that the disease free survival results of the instant method using MAGE-A3, MART-1, GalNacT, and PAX3 as markers are superior to the disease free survival results of Scoggins et al (Journal of Clinical Oncology, 2006, 24(16):2849-2856) using MAGE-A3, MART-1, Tyrosinase, and GP100 as markers. Applicant further cites the post-filing teachings of Hillari et al (Ann Surg

Oncol, 2009, 16:177-185) and argues that Hillari et al teaches that GalNact has no predictive value in discriminating positive and cancer free lymph nodes and the predictive value of PAX3 is marginal at best. Applicant further argues that the combination of two markers from a non-predictive panel (MAGE-A3, MART-1), a non-discriminating marker (GalNAcT), and a marginally discriminating marker (PAX3) do not logically sum to the disease free survival results of the present invention. Applicant further argues that the whole is much greater than the sum of the parts with respect to the combination of MAGE-A3, MART-1, GalNAcT, and PAX3. In regards to claims 1 and 35, and their respective independent claims, Applicant argues that GalNAcT and PAX3 are capable of conferring remarkable prognostic power to an otherwise unremarkable combination of markers.

The amendments to the claims and the arguments found in the Reply of 5/7/10 have been carefully considered, but are not deemed persuasive. The Examiner agrees with the statement that the disease free survival results of the instant method using MAGE-A3, MART-1, GalNacT, and PAX3 as markers are superior to the disease free survival results of Scoggins et al using MAGE-A3, MART-1, Tyrosinase, and GP100 as markers.

In regard to the citation of the post-filing teachings of Hillari et al, argument that Hillari et al teaches that GalNAcT has no predictive value in discriminating positive and cancer free lymph nodes and the predictive value of PAX3 is marginal at best, and that GalNAcT and PAX3 are capable of conferring remarkable prognostic power to an otherwise unremarkable combination of markers, the instant rejection is based on what

would have been obvious *at the time the invention was made*. Therefore, the post-filing teachings of Hillari et al would not be used as guidance to determine what was obvious at the time the invention was made. The pre-filing publication Hoon et al teaches that GalNAcT is a marker of melanoma cancer cells for use in discriminating positive and cancer free lymph nodes (see column 2 line 53 to column 3 line 36, in particular). Further, the pre-filing teachings of Kuo et al (Clinical Cancer Research, 1998, 4(411-418) support the teachings of Hoon et al by demonstrating that GalNAcT RNA in blood and lymph nodes is an indicator of advanced stage melanoma tumors (see pages 413-414, in particular). Further, the pre-filing publication of Scholl et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from one of a variety of locations from a patient, amplifying nucleic acid targets from a panel of marker genes comprising PAX-3 and MAGE-A3, and detecting the presence or absence of the nucleic acid targets (Table 1 and Table 2, in particular). Therefore, based on the teachings at the time the invention was made, it would have been obvious to use GalNAcT and PAX3 as markers to discriminate positive and cancer free samples, such as lymph nodes.

In regards to the argument that the combination of two markers from a non-predictive panel (MAGE-A3, MART-1), a non-discriminating marker (GalNAcT), and a marginally discriminating marker (PAX3) do not logically sum to the disease free survival results of the present invention, use of MARGE-A3, GalNAcT, and PAX3 is obvious based on the teachings at the time the invention was made for the reasons stated above.

In regards to the argument that the whole is much greater than the sum of the parts with respect to the combination of MAGE-A3, MART-1, GalNAcT, and PAX3, Hoon et al clearly teaches multiple markers are to be used to detect metastatic melanoma (lines 15-20 of page 3, claim 1, and claim 5 of Hoon et al, in particular). Further, Hoon et al (J Clin Oncol, 1995, 13(18): 2109-2116) teaches "the use of more than one marker can verify the presence of occult melanoma cells and significantly increase the sensitivity to detect cell that express few or no copies of tyrosinase mRNA ... The number of markers detected in individual patients was significantly correlated with disease stage and progression. This suggests that there could be higher expression of individual marker genes, greater heterogeneity of tumor cells, or more tumor cells in circulation at advanced stages of disease" *well before* the filing date of the instant application (see right column of page 2114, in particular). Therefore, Hoon et al clearly teaches assays detecting numerous markers of metastatic melanoma are preferred. Further, "synergistic" results have not been demonstrated by applicant.

Claims 1-5, 7, 10, 35-38 and 40-47 remain rejected and claims 48-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoon et al (US Patent 6,057,105; 5/2/00) in view of Scholl et al (2/01, Cancer Research, 61:823-826) as applied to claims 1-3, 5, 7, 10, 35-36, 38, and 40-47 above, and further in view of Johansson et al (2000, Clinical Chemistry, 46(7): 921-927) for the reasons stated in the Office Action of 11/4/09, for the reasons stated in the Office Action of 4/15/10 and for the reasons set-forth below.

Teaching of claims 1-3, 5, 7, 10, 35-36, 38, and 40-47 by Hoon et al in view of Scholl et al is discussed above.

The combined teachings of Hoon et al and Scholl et al do no specifically teach using qRT-PCR to detect PAX3, MAGE-A3, and GalNacT expression. However, these deficiencies are made up in the teachings of Johansson et al.

Johansson et al teaches a reproducible method comprising performing qRT to quantitatively detect copy number of mRNA markers of melanoma in blood samples (pages 922-923, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to use qRT to detect expression of marker genes when performing the method of detecting and characterizing metastatic melanoma as taught by the combined teachings of Hoon et al and Scholl et al because qRT is a quantitative method of detecting specific mRNA transcripts (Figure 4 of Johansson et al, in particular) which would streamline the method and facilitate comparison between multiple experiments and remove discrepancies relying on visual inspection of an electrophoresis gel (see Hoon et al at lines 13-14 of column 17, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success when using qRT to detect expression of marker genes when performing the method taught by the combined teachings of Hoon et al and Scholl et al because Johansson et al demonstrates that qRT quantitatively detects transcripts which are mRNA markers of melanoma in body fluid samples (pages 922-923, in particular).

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

In the Reply of 5/7/10, Applicant repeats arguments that have been addressed above.

Summary

No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean E Aeder/
Primary Examiner, Art Unit 1642